

**AMENDMENTS TO THE CLAIMS:**

Please amend the claims as follows:

1. (Currently Amended) A method of ~~preventing or~~ treating arthritis, comprising administering to a patient, as an active ingredient, an antibody which specifically binds to FGF-8 to inhibit activity of FGF-8.

2. (Previously Presented) The method according to claim 1, wherein the antibody which specifically binds to FGF-8 to inhibit activity of FGF-8 is a monoclonal antibody.

3. (Currently Amended) The method according to claim 2, wherein the monoclonal antibody is an antibody selected from an antibody produced by a hybridoma, a humanized antibody and an antigen-binding [[antibody]] fragment thereof.

4. (Withdrawn) The method according to claim 3, wherein the hybridoma is hybridoma KM1334 (FERM BP-5451).

5. (Previously Presented) The method according to claim 3, wherein the humanized antibody is a human chimeric antibody or a human complementarity determining region (CDR)-grafted antibody.

6. (Previously Presented) The method according to claim 5, wherein the human chimeric antibody comprises an antibody heavy chain variable region (VH) and an antibody light chain variable region (VL) of a monoclonal antibody which specifically binds to FGF-8 to inhibit activity of FGF-8, and an antibody heavy chain constant region (CH) and an antibody light chain constant region (CL) of a human antibody.

7. (Withdrawn) The method according to claim 6, wherein the human chimeric antibody is any of the following human chimeric antibodies (a) to (c),

(a) a human chimeric antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 5,

(b) a human chimeric antibody in which VL comprises an amino acid sequence represented by SEQ ID NO: 6, and

(c) a human chimeric antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 5 and VL comprises an amino acid sequence represented by SEQ ID NO: 6.

8. (Withdrawn) The method according to claim 7, wherein the human chimeric antibody is a human chimeric antibody produced by transformant KM3034 (FERM BP-7836).

9. (Previously Presented) The method according to claim 5, wherein the human CDR-grafted antibody comprises CDRs of VH and VL of a monoclonal antibody which specifically binds to FGF-8 to inhibit activity of FGF-8 and CH and CL of a human antibody.

10. (Previously Presented) The method according to claim 9, wherein the human CDR-grafted antibody comprises CDRs of VH and VL of a monoclonal antibody which specifically binds to FGF-8 to inhibit activity of FGF-8, framework regions (FRs) of VH and VL of a human antibody and CH and CL of a human antibody.

11. (Currently Amended) The method according to claim 9, wherein the human CDR-grafted antibody is any of the following a human CDR-grafted antibodies ~~(a) to (c)~~,  
~~(a) a human CDR-grafted antibody in which CDR1, CDR2 and CDR3 of VH~~  
comprise amino acid sequences represented by SEQ ID NOS: 7, 8 and 9 respectively  
and r

~~(b) a human CDR-grafted antibody in which CDR1, CDR2 and CDR3 of VL~~  
comprise amino acid sequences represented by SEQ ID NOS: 10, 11 and 12  
respectively, and

~~(c) a human CDR-grafted antibody in which CDR1, CDR2 and CDR3 of VH~~  
comprise amino acid sequences represented by SEQ ID NOS: 7, 8 and 9 respectively  
and CDR1, CDR2 and CDR3 of VL comprise amino acid sequences represented by  
SEQ ID NOS: 10, 11 and 12 respectively.

12. (Withdrawn) The method according to claim 9, wherein the human CDR-grafted antibody is any of the following human CDR-grafted antibodies (a) to (c),

(a) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 in which at least one or more amino acid residue selected from Lys at position 12, Lys at position 13, Ala at position 40, Pro at position 41, Met at position 48, Val at position 68, Ile at position 70, Thr at position 74, Thr at position 76, Glu at position 82, Ser at position 84, Arg at position 87 and Tyr at position 95 is replaced with another amino acid residue,

(b) a human CDR-grafted antibody in which VL comprises an amino acid sequence represented by SEQ ID NO: 19 in which at least one or more amino acid residue selected from Ile at position 2, Val at position 3, Thr at position 14, Pro at position 15, Gln at position 50, Leu at position 51 and Tyr at position 92 is replaced with another amino acid residue, and

(c) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 in which at least one or more amino acid residue selected from Lys at position 12, Lys at position 13, Ala at position 40, Pro at position 41, Met at position 48, Val at position 68, Ile at position 70, Thr at position 74, Thr at position 76, Glu at position 82, Ser at position 84, Arg at position 87 and Tyr at position 95 is replaced with another amino acid residue, and VL comprises an amino acid sequence represented by SEQ ID NO: 19 in which at least one or more amino acid residue selected from Ile at position 2, Val at position 3, Thr at position 14, Pro at

position 15, Gln at position 50, Leu at position 51 and Tyr at position 92 is replaced with another amino acid residue.

13. (Currently Amended Presented) The method according to claim 9, wherein the human CDR-grafted antibody is ~~a any of the following~~ human CDR-grafted antibodies (a) to (c),

(a) ~~a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 or 20~~ and,

(b) ~~a human CDR-grafted antibody in which VL comprises an amino acid sequence represented by SEQ ID NO: 19, 21, 42, 43, 44, 45, 46, 47, 50 or 51,~~ and

(c) ~~a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 or 20 and VL comprises an amino acid sequence represented by SEQ ID NO: 19, 21, 42, 43, 44, 45, 46, 47, 50 or 51.~~

14. (Previously Presented) The method according to claim 13, wherein the human CDR-grafted antibody is any of the following human CDR-grafted antibodies (a) to (c),

(a) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 and VL comprises an amino acid sequence represented by SEQ ID NO: 21,

(b) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 and VL comprises an amino acid sequence represented by SEQ ID NO: 44, and

(c) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 and VL comprises an amino acid sequence represented by SEQ ID NO: 50.

15. (Previously Presented) The method according to claim 9, wherein the human CDR-grafted antibody is any of the following human CDR-grafted antibodies (a) to (c),

(a) a human CDR-grafted antibody produced by transformant KM8037 (FERM BP-8084),

(b) a human CDR-grafted antibody produced by transformant KM8035 (FERM BP-8082), and

(c) a human CDR-grafted antibody produced by transformant KM8036 (FERM BP-8083).

16. (Currently Amended) The method according to claim 3, wherein the antigen-binding fragment thereof ~~antibody fragment~~ is an antigen-binding fragment ~~antibody fragment~~ selected from Fab, Fab', F(ab')<sub>2</sub>, a single chain antibody (scFv), a dimerized variable region (V region) fragment (diabody), a disulfide-stabilized V region fragment (dsFv) and a CDR-containing peptide.

17. (Withdrawn) A diagnostic agent of arthritis comprising an antibody which specifically binds to FGF-8 as an active ingredient.

18. (Withdrawn) The diagnostic agent according to claim 17, wherein the antibody which specifically binds to FGF-8 is a polyclonal antibody or a monoclonal antibody.

19. (Withdrawn – Currently Amended) The diagnostic agent according to claim 18, wherein the monoclonal antibody is an antibody selected from an antibody produced by a hybridoma, a humanized antibody and an [[antibody]]antigen-binding fragment thereof.

20. (Withdrawn) The diagnostic agent according to claim 19, wherein the hybridoma is hybridoma KM1334 (FERM BP-5451).

21. (Withdrawn) The diagnostic agent according to claim 19, wherein the humanized antibody is a human chimeric antibody or a human CDR-grafted antibody.

22. (Withdrawn) The diagnostic agent according to claim 21, wherein the human chimeric antibody is a human chimeric antibody comprising VH and VL of a monoclonal antibody which specifically binds to FGF-8 and CH and CL of a human antibody.

23. (Withdrawn) The diagnostic agent according to claim 22, wherein the human chimeric antibody is any of the following human chimeric antibodies (a) to (c),

(a) a human chimeric antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 5,

(b) a human chimeric antibody in which VL comprises an amino acid sequence represented by SEQ ID NO: 6, and

(c) a human chimeric antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 5 and VL comprises an amino acid sequence represented by SEQ ID NO: 6.

24. (Withdrawn) The diagnostic agent according to claim 23, wherein the human chimeric antibody is a human chimeric antibody produced by transformant KM3034 (FERM BP-7836).

25. (Withdrawn) The diagnostic agent according to claim 21, wherein the human CDR-grafted antibody is a human CDR-grafted antibody comprising CDRs of VH and VL of a monoclonal antibody which specifically binds to FGF-8 and CH and CL of a human antibody.

26. (Withdrawn) The diagnostic agent according to claim 25, wherein the human CDR-grafted antibody is a human CDR-grafted antibody comprising CDRs of VH and



VL of a monoclonal antibody which specifically binds to FGF-8, FRs of VH and VL of a human antibody and CH and CL of a human antibody.

27. (Withdrawn) The diagnostic agent according to claim 25, wherein the human CDR-grafted antibody is any of the following human CDR-grafted antibodies (a) to (c),

(a) a human CDR-grafted antibody in which CDR1, CDR2 and CDR3 of VH comprise amino acid sequences represented by SEQ ID NOS: 7, 8 and 9 respectively,

(b) a human CDR-grafted antibody in which CDR1, CDR2 and CDR3 of VL comprise amino acid sequences represented by SEQ ID NOS: 10, 11 and 12 respectively, and

(c) a human CDR-grafted antibody in which CDR1, CDR2 and CDR3 of VH comprise amino acid sequences represented by SEQ ID NOS: 7, 8 and 9 respectively, and CDR1, CDR2 and CDR3 of VL comprise amino acid sequences represented by SEQ ID NOS: 10, 11 and 12 respectively.

28. (Withdrawn) The diagnostic agent according to claim 25, wherein the human CDR-grafted antibody is any of the following human CDR-grafted antibodies (a) to (c),

(a) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 in which at least one or more amino acid residue selected from 1 Lys at position 12, Lys at position 13, Ala at position 40, Pro at position 41, Met at position 48, Val at position 68, Ile at position 70, Thr at position 74,

Thr at position 76, Glu at position 82, Ser at position 84, Arg at position 87 and Tyr at position 95 is replaced with another amino acid residue,

(b) a human CDR-grafted antibody in which VL comprises an amino acid sequence represented by SEQ ID NO: 19 in which at least one or more amino acid residue selected from Ile at position 2, Val at position 3, Thr at position 14, Pro at position 15, Gln at position 50, Leu at position 51 and Tyr at position 92 is replaced with another amino acid residue, and

(c) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 in which at least one or more amino acid residue selected from Lys at position 12, Lys at position 13, Ala at position 40, Pro at position 41, Met at position 48, Val at position 68, Ile at position 70, Thr at position 74, Thr at position 76, Glu at position 82, Ser at position 84, Arg at position 87 and Tyr at position 95 is replaced with another amino acid residue, and VL comprises an amino acid sequence represented by SEQ ID NO: 19 in which at least one or more amino acid residue selected from Ile at position 2, Val at position 3, Thr at position 14, Pro at position 15, Gln at position 50, Leu at position 51 and Tyr at position 92 is replaced with another amino acid residue.

29. (Withdrawn) The diagnostic agent according to claim 25, wherein the human CDR-grafted antibody is any of the following human CDR-grafted antibodies (a) to (c),

(a) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 or 20,

(b) a human CDR-grafted antibody in which VL comprises an amino acid sequence represented by SEQ ID NO: 19, 21, 42, 43, 44, 45, 46, 47, 50 or 51, and

(c) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 or 20 and VL comprises an amino acid sequence represented by SEQ ID NO: 19, 21, 42, 43, 44, 45, 46, 47, 50 or 51.

30. (Withdrawn) The diagnostic agent according to claim 29, wherein the human CDR-grafted antibody is any of the following human CDR-grafted antibodies (a) to (c),

(a) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 and VL comprises an amino acid sequence represented by SEQ ID NO: 21,

(b) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 and VL comprises an amino acid sequence represented by SEQ ID NO: 44, and

(c) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 and VL comprises an amino acid sequence represented by SEQ ID NO: 50.

31. (Withdrawn) The diagnostic agent according to claim 25, wherein the human CDR-grafted antibody is any of the following human CDR-grafted antibodies (a) to (c),

(a) a human CDR-grafted antibody produced by transformant KM8037 (FERM BP-8084),

(b) a human CDR-grafted antibody produced by transformant KM8035 (FERM BP-8082), and

(c) a human CDR-grafted antibody produced by transformant KM8036 (FERM BP-8083).

32. (Withdrawn) The diagnostic agent according to claim 19, wherein the antibody fragment is an antibody fragment selected from Fab, Fab', F(ab')<sub>2</sub>, a single chain antibody (scFv), a dimerized V region fragment (diabody), a disulfide-stabilized V region fragment (dsFv) and a CDR-containing peptide.

33. (Withdrawn) A diagnostic method for judging arthritis, which comprises detecting and/or determining FGF-8 in a sample using an antibody which specifically binds to FGF-8.

34. (Withdrawn) The diagnostic method according to claim 33, wherein the antibody which specifically binds to FGF-8 is a polyclonal antibody or a monoclonal antibody.

35. (Withdrawn – Currently Amended) The diagnostic method according to claim 34, wherein the monoclonal antibody is an antibody selected from an antibody produced

by a hybridoma, a humanized antibody and an [[antibody]]antigen-binding fragment thereof.

36. (Withdrawn) The diagnostic method according to claim 35, wherein the hybridoma is hybridoma KM1334 (FERM BP-5451).

37. (Withdrawn) The diagnostic method according to claim 35, wherein the humanized antibody is a human chimeric antibody or a human CDR-grafted antibody.

38. (Withdrawn) The diagnostic method according to claim 37, wherein the human chimeric antibody is a human chimeric antibody comprising VH and VL of a monoclonal antibody which specifically binds to FGF-8 and CH and CL of a human antibody.

39. (Withdrawn) The diagnostic method according to claim 38, wherein the human chimeric antibody is any of the following human chimeric antibodies (a) to (c),

(a) a human chimeric antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 5,

(b) a human chimeric antibody in which VL comprises an amino acid sequence represented by SEQ ID NO: 6, and

(c) a human chimeric antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 5 and VL comprises an amino acid sequence represented by SEQ ID NO: 6.

40. (Withdrawn) The diagnostic method according to claim 39, wherein the human chimeric antibody is a human chimeric antibody produced by transformant KM3034 (FERM BP-7836).

41. (Withdrawn) The diagnostic method according to claim 37, wherein the human CDR-grafted antibody is a human CDR-grafted antibody comprising CDRs of VH and VL of a monoclonal antibody which specifically binds to FGF-8 and CH and CL of a human antibody.

42. (Withdrawn) The diagnostic method according to claim 41, wherein the human CDR-grafted antibody is a human CDR-grafted antibody comprising CDRs of VH and VL of a monoclonal antibody which specifically binds to FGF-8, FRs of VH and VL of a human antibody and CH and CL of a human antibody.

43. (Withdrawn) The diagnostic method according to claim 41, wherein the human CDR-grafted antibody is any of the following human CDR-grafted antibodies (a) to (c),

(a) a human CDR-grafted antibody in which CDR1, CDR2 and CDR3 of VH comprise amino acid sequences represented by SEQ ID NOS: 7, 8 and 9 respectively,

(b) a human CDR-grafted antibody in which CDR1, CDR2 and CDR3 of VL comprise amino acid sequences represented by SEQ ID NOS: 10, 11 and 12 respectively, and

(c) a human CDR-grafted antibody in which CDR1, CDR2 and CDR3 of VH comprise amino acid sequences represented by SEQ ID NOS: 7, 8 and 9 respectively, and CDR1, CDR2 and CDR3 of VL comprise amino acid sequences represented by SEQ ID NOS: 10, 11 and 12 respectively.

44. (Withdrawn) The diagnostic method according to claim 41, wherein the human CDR-grafted antibody is any of the following human CDR-grafted antibodies (a) to (c),

(a) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 in which at least one or more amino acid residue selected from Lys at position 12, Lys at position 13, Ala at position 40, Pro at position 41, Met at position 48, Val at position 68, Ile at position 70, Thr at position 74, Thr at position 76, Glu at position 82, Ser at position 84, Arg at position 87 and Tyr at position 95 is replaced with another amino acid residue,

(b) a human CDR-grafted antibody in which VL comprises an amino acid sequence represented by SEQ ID NO: 19 in which at least one or more amino acid residue selected from Ile at position 2, Val at position 3, Thr at position 14, Pro at

position 15, Gln at position 50, Leu at position 51 and Tyr at position 92 is replaced with another amino acid residue, and

(c) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 in which at least one or more amino acid residue selected from Lys at position 12, Lys at position 13, Ala at position 40, Pro at position 41, Met at position 48, Val at position 68, Ile at position 70, Thr at position 74, Thr at position 76, Glu at position 82, Ser at position 84, Arg at position 87 and Tyr at position 95 is replaced with another amino acid residue, and VL comprises an amino acid sequence represented by SEQ ID NO: 19 in which at least one or more amino acid residue selected from Ile at position 2, Val at position 3, Thr at position 14, Pro at position 15, Gln at position 50, Leu at position 51 and Tyr at position 92 is replaced with another amino acid residue.

45. (Withdrawn) The diagnostic method according to claim 41, wherein the human CDR-grafted antibody is any of the following human CDR-grafted antibodies (a) to (c),

(a) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 or 20,

(b) a human CDR-grafted antibody in which VL comprises an amino acid sequence represented by SEQ ID NO: 19, 21, 42, 43, 44, 45, 46, 47, 50 or 51, and



(c) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 or 20 and VL comprises an amino acid sequence represented by SEQ ID NO: 19, 21, 42, 43, 44, 45, 46, 47, 50 or 51.

46. (Withdrawn) The diagnostic method according to claim 45, wherein the human CDR-grafted antibody is any of the following human CDR-grafted antibodies (a) to (c),

(a) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 and VL comprises an amino acid sequence represented by SEQ ID NO: 21,

(b) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 and VL comprises an amino acid sequence represented by SEQ ID NO: 44, and

(c) a human CDR-grafted antibody in which VH comprises an amino acid sequence represented by SEQ ID NO: 18 and VL comprises an amino acid sequence represented by SEQ ID NO: 50.

47. (Withdrawn) The diagnostic method according to claim 41, wherein the human CDR-grafted antibody is any of the following human CDR-grafted antibodies (a) to (c),

(a) a human CDR-grafted antibody produced by transformant KM8037 (FERM BP-8084),

(b) a human CDR-grafted antibody produced by transformant KM8035 (FERM BP-8082), and

(c) a human CDR-grafted antibody produced by transformant KM8036 (FERM BP-8083).

48. (Withdrawn) The diagnostic method according to claim 35, wherein the antibody fragment is an antibody fragment selected from Fab, Fab', F(ab')<sub>2</sub>, a single-chain antibody (scFv), a dimerized V region fragment (diabody), a disulfide-stabilized V region fragment (dsFv) and a CDR-containing peptide.

49. (Previously Presented) A method of inhibiting joint destruction inhibitor comprising administering to a patient, as an active ingredient, an antibody which specifically binds to FGF-8 to inhibit activity of FGF-8.

50. (Previously Presented) A method of protecting cartilage comprising administering to a patient, as an active ingredient, an antibody which specifically binds to FGF-8 to inhibit activity of FGF-8.

51. (Previously Presented) A method of inhibiting growth of synovial membrane comprising administering to a patient, as an active ingredient, an antibody which specifically binds to FGF-8 to inhibit activity of FGF-8.